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pT1N1M0早期胃癌术后辅助治疗临床意义的探索

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摘　要

背景：pT1N1M0分期胃癌术后辅助治疗目前各大指南无统一共识。本研究的目的是确定辅助放化疗对pT1N1M0胃癌根治术后患者有无生存获益，分析影响pT1N1M0胃癌患者预后的危险因素。方法：从SEER数据库中选择2004年至2019年胃切除术后pT1N1M0 GC患者319例。采用Kaplan-Meier法和log-rank检验分析总生存率。采用Cox比例风险回归模型对影响pT1N1M0胃癌根治性切除患者预后的因素进行单变量和多变量分析。结果：生存分析显示术后辅助化疗(5年OS：52.4% vs. 75.8%，$p < 0.001$)和辅助放疗(5年OS: 59.9% vs. 71.9%，$p = 0.001$)可显著延长pT1N1M0胃癌患者的生存期。多因素Cox回归分析显示年龄($p = 0.001$)，原发部位($p = 0.009$)，检查淋巴结数量(ELNC) ($p = 0.007$)和辅助化疗($p = 0.006$)是与OS相关的独立预后因素。这些变量符合Cox回归比例风险假设检验($p > 0.05$)。结论：术后辅助化疗及辅助放疗能够改善pT1N1M0 GC患者OS，年龄、辅助化疗、肿瘤部位、ELNC是pT1N1M0胃癌预后的独立影响因素。

关键词

pT1N1M0，早期胃癌，预后，辅助化疗，辅助放疗

The Clinical Significance of Postoperative Adjuvant Therapy for pT1N1M0 Early Gastric Cancer

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Abstract

Background: Currently, there is no consensus on postoperative adjuvant therapy for pT1N1M0 gastric cancer in major guidelines. The aim of this study is to determine the survival benefit of adjuvant chemoradiotherapy in patients with pT1N1M0 gastric cancer after radical gastrectomy, and to analyze the risk factors affecting the prognosis of patients with pT1N1M0 gastric cancer. Methods: A total of 319 patients with pT1N1M0 GC after gastrectomy from 2004 to 2019 were selected from the SEER database. Kaplan-Meier method and log-rank test were used to analyze the overall survival rate. Univariate and multivariate analyses of prognostic factors of patients with pT1N1M0 gastric cancer after radical resection were performed using Cox proportional hazards regression model. Results: Survival analysis showed that postoperative adjuvant chemotherapy (5-year OS: 52.4% vs. 75.8%, p < 0.001) and adjuvant radiotherapy (5-year OS: 59.9% vs. 71.9%, p = 0.001) could significantly prolong the survival of patients with pT1N1M0 gastric cancer. Multivariate Cox regression analysis showed that age (p = 0.001), primary site (p = 0.009), number of examined lymph node count (ELNC) (p = 0.007) and adjuvant chemotherapy (p = 0.006) were independent prognostic factors associated with OS. These variables were in accordance with the Cox regression proportional hazards hypothesis test (p > 0.05). Conclusions: Postoperative adjuvant chemotherapy and radiotherapy can improve the OS of patients with pT1N1M0 GC. Age, adjuvant chemotherapy, tumor location, and ELNC are independent prognostic factors for pT1N1M0 gastric cancer.

Keywords

pT1N1M0, Early Gastric Cancer, Prognosis, Adjuvant Chemotherapy, Adjuvant Radiotherapy

1. 引言

根据美国 AJCC 分期系统及日本胃癌分类指南(第三版)，pT1N1M0 为局限于粘膜层或黏膜下层并伴有 1 个或 2 个淋巴结转移[1] [2]。虽然 pT1N1M0 患者根治性切除术后预后极佳，然而仍有约 3.1%~4.7%患者出现复发转移，包括肝、骨、肺和肾上腺等血行转移、远端淋巴结复发、残胃复发、腹膜复发等[3]-[7]。根据 CSCO 指南及 NCCN 指南，pT1N10 胃癌患者术后应行术后辅助治疗。然而，日本胃癌治疗指南对于分期为 pT1N1M0 的早期胃癌患者推荐术后仅随访观察[8]。pT1N1M0 术后辅助化疗及辅助放疗的应用目前各大指南未形成统一共识。目前临床工作中，对 I 期胃癌，特别是 pT1N1M0 分期胃癌的术后辅助治疗，主要由外科学或肿瘤专家进行经验性治疗。

因此，本研究回顾性分析 SEER 数据库 319 例 pT1N1M0 早期胃癌术后患者，以确定 pT1N1M0 患者的辅助治疗的临床意义，分析影响 pT1N1M0 胃癌独立预后危险因素，筛选高危人群，为临床治疗方案选择提供参考。

2. 材料和方法

2.1. 患者来源

我们从 SEER 数据库(https://www.seer.cancer.gov/)“Incidence-SEER Research Data, 17 Registries, Nov

2023 Sub (2000~2021)”数据集中下载 pT1N1M0 胃癌患者的数据。该数据库包含约 35%美国人口的癌症流行病学和人口统计学回顾性研究信息。由于 SEER 数据库是公开的，不需要知情同意，因此本研究免除了本机构伦理委员会的审查。本研究纳入 2004~2019 年根治性胃切除术后(代码范围：RX Summ--Surg Prim Site (1998+) = 30 − 52) [9]诊断为 pT1N1M0 早期胃癌的患者。

纳入标准：(i) 原发部位为胃；(ii) 显微镜下细胞或组织学病理诊断明确；(iii) 分期符合 pT1N1M0；(iv) 确诊为单原发肿瘤；

排除标准：(i) 未接受根治性手术；(ii) 阳性淋巴结非 1~2 个；(iii) 伴有远处转移；(iv) 术前接受综合治疗；(iv) 在切除前或切除中接受放疗和/或化疗；(v) 年龄未满 18 周岁；(vi) 生存结果未知；(vii) 检查区域淋巴结未知；(viii) 肿瘤大小无确切数值。

根据上述标准，最终 319 例患者被纳入本研究。从 SEER 数据库中提取以下人口统计学和病理学特征:种族、性别、诊断年份、年龄、原发肿瘤部位、组织类型、肿瘤大小、检查的区域淋巴结数量、阳性区域淋巴结数量、辅助放疗和辅助化疗情况、生存情况。

2.2. 统计学方法

通过 ROC 曲线确定检查的淋巴结数量(ELNC)的最佳临界值。治疗相关包括放疗(有，没有/未知)，化疗(有，没有/未知)。本研究以 OS 作为研究终点，定义为诊断至最后一次随访或任何原因死亡的时间。采用 Kaplan-Meier (K-M)计算 OS，并通过 log-rank 检验可信度。使用卡方检验或 Fisher’s 精确检验比较分类变量。采用 Cox 比例风险回归模型对影响 pT1N1M0 胃癌根治性切除患者预后的因素进行单变量和多变量分析。在我们的研究中，根据首次手术后是否给予辅助化疗，将患者分为化疗(CTx)和非化疗(non-CTx)两组。根据是否给予辅助放疗，将患者分为放疗(RTx)和非放疗(non-RTx)两组。本研究 GraphPad Prism 版本为 8.0.2，生存分析的统计分析采用 SPSS (v.26)软件。双侧 $p < 0.05$ 表示差异有统计学意义。

3. 研究结果

3.1. 基线特征

共有 319 例患者符合纳入和排除标准，纳入本研究。ROC 曲线下面积显示检查的淋巴结数量最佳截断值为 16。纳入研究的所有患者的基线特征见表 1。诊断年份以 2004~2009 为主(139 例，43.6%)。65 岁以上患者 205 例(64.3%)，65 岁以下的患者 114 例(35.7%)，男性患者 175 例(54.9%)，女性患者 144 例(45.1%)。白种人 189 例(59.2%)，黑种人 35 例(11.0%)。90 例肿瘤部位位于胃底和贲门(28.2%)，109 例位于胃窦和幽门(34.2%)，120 例位于其余部位(34.6%)。组织学类型中腺癌 241 例(75.5%)，印戒细胞癌 50 例(15.7%)。肿瘤大小以<20 mm 为主(128 例，40.1%)，阳性淋巴结 1 个的患者有 205 例(64.3%)，2 个阳性淋巴结转移的患者有 114 例(35.7%)，大多数淋巴结检查数量<16 (177 例，55.5%)。其中，接受辅助化疗的患者 163 例(51.1%)，未接受辅助化疗的患者 156 例(48.9%)。119 例(37.3%)患者接受了辅助放疗，200 例(62.7%)未接受辅助放疗。

纳入所有患者的平均生存时间为 117.4 个月(95% CI: 107.2~127.5)，中位生存时间为 123.0 个月(95% CI: 94.7~151.3)。

Table 1. Baseline characteristics of patients with pT1N1M0 gastric cancer after surgery in the SEER database
表 1. SEER 数据库 pT1N1M0 胃癌术后患者的基线特征

Characteristic	Total SEER (n = 319)	Characteristic	Total SEER (n = 319)
Year of diagnosis		Histology	

续表

2004~2009	139 (43.6)	Adenocarcinoma	241 (75.5)
2010~2014	113 (35.4)	signet-ring cell carcinoma	50 (15.7)
2015~2019	67 (21.0)	Others	28 (8.8)
Age		ELNC	
<65	114 (35.7)	<16	177 (55.5)
≥65	205 (64.3)	≥16	142 (44.5)
Gender		Tumor_size	
Female	144 (45.1)	≤20 mm	128 (40.1)
Male	175 (54.9)	≤30mm	79 (24.8)
Race		>30 mm	112 (35.1)
White	189 (59.2)	Chemotherapy	
Black	35 (11.0)	None/Unknown	156 (48.9)
Others	95 (29.8)	Yes	163 (51.1)
Primary site		Radiotherapy	
Fundus and cardia	90 (28.2)	None/Unknown	200 (62.7)
Antrum and pylorus	109 (34.2)	Yes	119 (37.3)
Others	120 (37.6)		
pLNs			
1	205 (64.3)		
2	114 (35.7)		

Abbreviations: ELNC, examined lymph node count; pLNs, positive lymph nodes.

3.2. 辅助性放化疗对预后的影响

与未化疗组相比，辅助化疗组患者年龄以≥65 岁为主，未行放疗比例较高，1 个阳性淋巴结转移比例较高，胃底和贲门比例较低，差异与统计学意义($p < 0.05$) (表 2)。与未放疗组相比，辅助放疗组患者年龄以≥65 岁为主，ELNC ≥ 16 比例较高，1 个阳性淋巴结转移比例较高。差异有统计学意义($p < 0.05$) (表 3)。生存分析显示术后 ACT (5 年 OS：52.4% vs. 75.8%，$p < 0.001$)和 ART (5 年 OS：59.9% vs. 71.9%，$p = 0.001$)可显著延长 T1N1 胃癌患者的生存期(图 1)。

Table 2. Clinicopathologic features of the CTx and non-CTx groups
表 2. CTx 组与 non-CTx 组的临床病理特征

Characteristic	CTx Group n (%)	Non-CTx Group n (%)	p value
Year of diagnosis			0.193
2004~2009	76 (48.7)	63 (38.7)	
2010~2014	50 (32.1)	63 (38.7)	
2015~2019	30 (19.2)	37 (22.7)	
Age			< 0.001
<65	29 (18.6)	85 (52.1)	
≥65	127 (81.4)	78 (47.9)	
Gender			0.420
Female	74 (47.4)	70 (42.9)	
Male	82 (52.6)	93 (57.1)	
Race			0.674
White	92 (59.0)	97 (59.5)	
Black	15 (9.6)	20 (12.3)	

续表

Others	49 (31.4)	46 (28.2)	
Primary site			0.080
Fundus and cardia	35 (22.4)	55 (33.7)	
Antrum and pylorus	58 (37.2)	51 (31.3)	
Others	63 (40.4)	57 (35.0)	
Histology			0.048
Adenocarcinoma	120 (76.9)	121 (74.2)	
signet-ring cell carcinoma	18 (11.5)	32 (19.6)	
Others	18 (11.5)	10 (6.1)	
ELNC			0.304
<16	82 (52.6)	95 (58.3)	
≥16	74 (47.4)	68 (41.7)	
Tumor_size			0.279
≤20 mm	61 (39.1)	67 (41.1)	
≤30mm	34 (21.8)	45 (27.6)	
>30 mm	61 (39.1)	51 (31.3)	
pLNs			0.023
1	110 (70.5)	95 (58.3)	
2	46 (29.5)	68 (41.7)	
Radiotherapy			0.001
None/Unknown	147 (94.2)	53 (32.5)	
Yes	9 (5.8)	110 (67.5)	

Abbreviations: CTx, chemotherapy; ELNC, examined lymph node count; pLNs, positive lymph nodes.

Table 3. Clinicopathologic characteristics of the RTx and non-RTx groups
表 3. RTx 组与 non-RTx 组的临床病理特征

Characteristic	RTx Group n (%)	Non-RTx Group n (%)	p value
Year of diagnosis			0.131
2004~2009	82 (41.0)	57 (47.9)	
2010~2014	69 (34.5)	44 (37.0)	
2015~2019	49 (24.5)	18 (15.1)	
Age			0.001
<65	58 (29.0)	56 (47.1)	
≥65	142 (71.0)	63 (52.9)	
Gender			0.272
Female	95 (47.5)	49 (41.2)	
Male	105 (52.5)	70 (58.8)	
Race			0.345
White	120 (60.0)	69 (58.0)	
Black	25 (12.5)	10 (8.4)	
Others	55 (27.5)	40 (33.6)	
Primary site			0.756
Fundus and cardia	54 (27.0)	36 (30.3)	
Antrum and pylorus	71 (35.5)	38 (31.9)	
Others	75 (37.5)	45 (37.8)	
Histology			0.168
Adenocarcinoma	149 (74.5)	92 (77.3)	

续表

signet-ring cell carcinoma	29 (14.5)	21 (17.6)	
Others	22 (11.0)	6 (5.0)	
ELNC			0.001
<16	97 (48.5)	80 (67.2)	
≥16	103 (51.5)	39 (32.8)	
Tumor_size			0.371
≤20 mm	80 (40.0)	48 (40.3)	
≤30mm	45 (22.5)	34 (28.6)	
>30 mm	75 (37.5)	37 (31.1)	
pLNs			0.006
1	140 (70.0)	65 (54.6)	
2	60 (30.0)	54 (45.4)	
Chemotherapy			< 0.001
None/Unknown	147 (73.5)	9 (7.6)	
Yes	53 (26.5)	110 (92.4)	

Abbreviations: RTx, radiotherapy; ELNC, examined lymph node count; pLNs, positive lymph nodes.

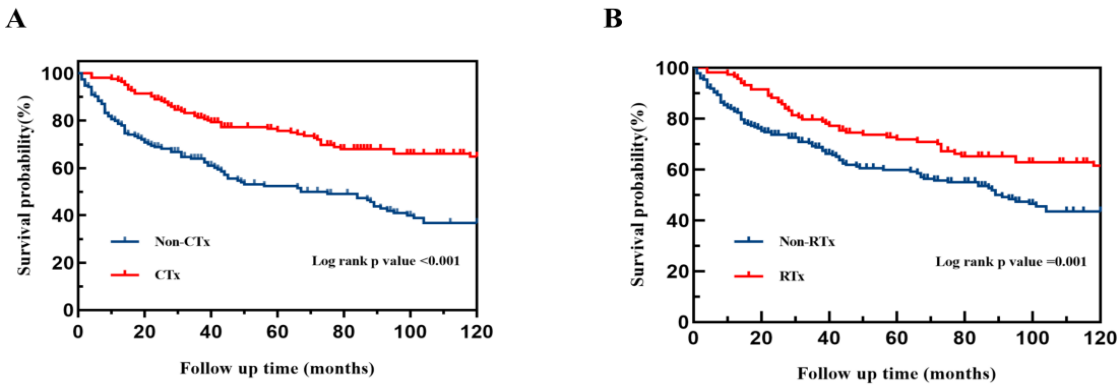

Figure 1. (A) K-M curves of patients with pT1N1M0 gastric cancer after operation with adjuvant chemotherapy and without adjuvant chemotherapy; (B) K-M curves of patients with pT1N1M0 gastric cancer after operation with adjuvant radiotherapy and without adjuvant radiotherapy

图 1. (A) pT1N1M0 期胃癌患者术后辅助化疗与未辅助化疗的 K-M 曲线；(B) pT1N1M0 期胃癌患者术后辅助放疗与未辅助放疗的 K-M 曲线

3.3. T1N1M0 胃癌预后的影响因素

对 319 例 pT1N1M0 的早期胃癌患者进行单因素 Cox 回归分析，年龄、诊断年份、ELNC、化疗和放疗为显著变量($p < 0.05$) (表 4)。将 $p < 0.1$ 的变量纳入多因素回归分析。多因素 Cox 回归分析显示年龄($p = 0.001$)，原发部位($p = 0.009$)，ELNC ($p = 0.007$)和辅助化疗($p = 0.006$)是与 OS 相关的独立预后因素。这些变量符合 Cox 回归比例风险假设检验($p > 0.05$) (图 2)。

Table 4. Univariate and multivariate regression analysis of prognostic factors in patients with pT1N1M0 gastric cancer

表 4. 影响 pT1N1M0 期胃癌患者预后的单因素和多因素回归分析

Characteristic	Univariate analysis			Multivariate analysis		
	HR	95% CI	p value	HR	95% CI	p value
Year of diagnosis			0.085			0.298

续表

2004~2009	Ref			Ref		
2010~2014	0.860	0.607~1.220	0.398	1.033	0.718~1.487	0.861
2015~2019	0.523	0.293~0.931	**0.028**	0.649	0.360~1.173	0.162
Age			**<0.001**			**0.001**
<65	Ref			Ref		
≥65	2.603	1.784~3.799	**<0.001**	2.082	1.377~3.148	0.001
Gender			0.115			
Female	Ref					
Male	1.292	0.940~1.778	0.115			
Race			0.227			0.184
White	Ref			Ref		
Black	0.983	0.580~1.667	0.949	1.145	0.815~2.458	0.217
Others	0.729	0.507~1.049	0.089	0.820	0.562~1.197	0.304
Primary site			0.149			**0.009**
Fundus and cardia	Ref			Ref		
Antrum and pylorus	0.685	0.461~1.017	0.060	0.540	0.356~0.819	0.004
Others	0.763	0.524~1.110	0.158	0.615	0.414~0.913	0.016
Histology			0.154			
Adenocarcinoma	Ref					
signet-ring cell carcinoma	0.751	0.481~1.172	0.207			
Others	0.578	0.293~1.138	0.113			
ELNC			**0.007**			**0.007**
<16	Ref					
≥16	0.635	0.455~0.886	0.007	0.623	0.442~0.879	0.007
Tumor_size			0.352			
≤20 mm	Ref					
≤30mm	1.139	0.774~1.675	0.509			
>30 mm	0.845	0.584~1.222	0.370			
pLNs			0.415			
1	Ref					
2	0.871	0.625~1.214	0.415			
Chemotherapy			**<0.001**			**0.006**
None/Unknown	Ref			Ref		
Yes	0.429	0.310~0.593	<0.001	0.501	0.306~0.820	0.006
Radiotherapy			**0.001**			0.968
None/Unknown	Ref			Ref		
Yes	0.572	0.408~0.801	0.001	0.990	0.608~1.613	0.968

Abbreviations: HR, hazard ratio; CI, confidence interval; ELNC, examined lymph nodes count; pLNs, positive lymph nodes.

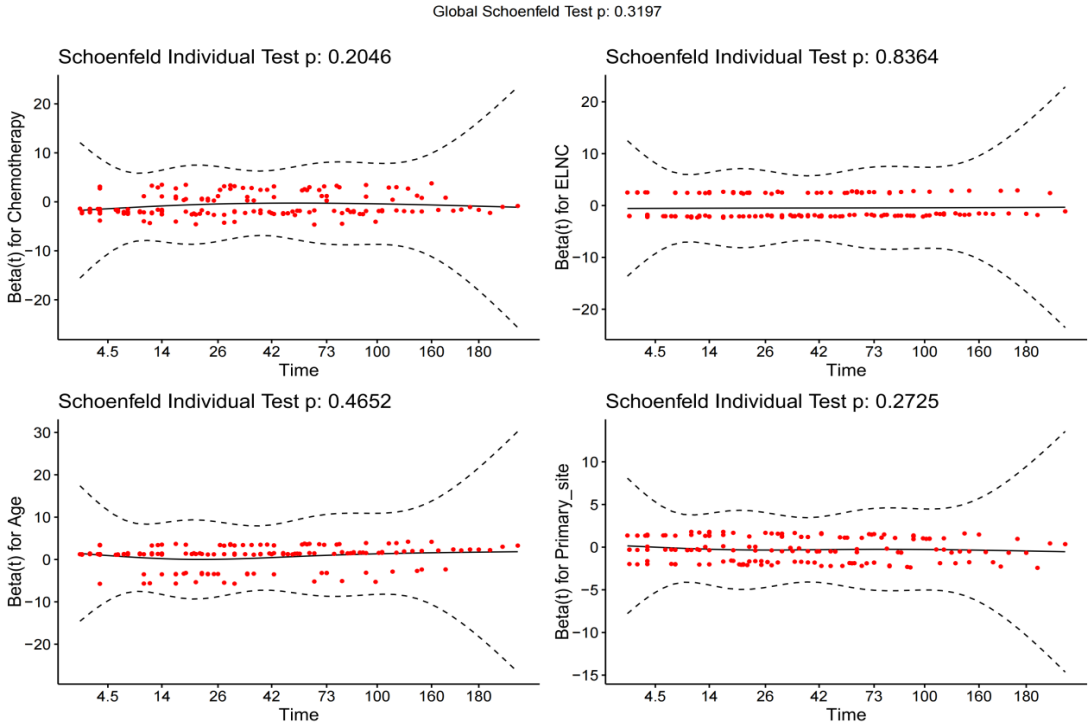

Figure 2. Risk hypothesis test of Cox regression proportion for chemotherapy, ELNC, age and primary site (p > 0.05)
图 2. 化疗、ELNC、年龄、原发部位符合 Cox 回归比例风险假设检验(p > 0.05)

4. 讨论

既往研究表明，与淋巴结阴性的早期胃癌相比，伴有淋巴结转移的早期胃癌复发率(10.6%~14.8%)明显升高[10]-[12]。因此，一些研究者建议对淋巴结阳性的早期胃癌进行辅助治疗，以避免手术切除后肿瘤复发。进展期胃癌术后辅助化疗的获益明确。ACTSGC 研究[13]、CLASSIC 研究[14]、JACCRO GC-07 研究[15]、ARTIST/ARTIST2 [16]研究等大型临床试验，已证实 II 期及以上(pT1N2-3)胃癌患者可从术后辅助化疗中获益。由于 I 期胃癌患者预后良好，大多数研究胃癌术后化疗疗效的临床试验未纳入评估包括 pT1N1M0 在内的 I 期患者。INT-0116 试验纳入了 IB 期至 IV 期胃癌患者进行 III 期临床研究，研究显示辅助放化疗显著降低了总体复发率和局部区域复发率，然而未对 IB 期进行单独亚组分析[17]。对于 I 期胃癌，尤其是 pT1N1M0，术后辅助治疗的必要性仍存在争议。本研究从 SEER 数据库中选取 319 例明确诊断为 pT1N1M0 的行胃癌根治术后的早期胃癌患者，统计分析 pT1N1M0 胃癌患者的 5 年 OS，多因素分析探索影响 pT1N1M0 胃癌预后的独立危险因素，评估辅助治疗对术后生存的影响。

我们的研究结果表明，辅助化疗是影响 pT1N1M0 胃癌患者的独立预后危险因素。本研究结果支持既往在西方人群中进行的研究结论，辅助治疗能独立改善 pT1N1M0 胃癌患者 OS [18] [19]。然而，来自东方国家的几项研究显示，与单纯手术相比，辅助化疗和辅助放化疗对 pT1N1M0 肿瘤复发无任何肿瘤学益处[3] [20] [21]。我们认为这可能是由于东西方人群之间种族、年龄、肿瘤大小、组织学类型等临床病理因素差异或潜在生物学特征差异以及淋巴结清扫范围不同导致[22]，一定程度上会影响患者预后及辅助治疗决策的制定。尽管如此，在最新的一项基于中国人群的多心中回顾性研究，亚组分析显示辅助化疗对 pT1N1M0 胃癌有生存获益。大量研究表明，化疗可能改善 I 期 GC 高危患者的预后，即使包括 CA19-9 升高、淋巴结阳性、阳性淋巴血管浸润、淋巴结清扫不全、结外扩展等[23]-[25]，术后辅助治疗可能是改善高危 pT1N1M0 胃癌患者预后的合理方法。

在目前的研究中，我们发现辅助性放疗对 pT1N1M0 胃癌预后具有改善作用，然而不是影响早期胃癌的独立预后危险因素。有研究提出临床决策时可根据 Lauren 的分型及肿瘤分级推荐 RT 加 ACT [19]。作为一种局部治疗，放射治疗还可能有一定的毒副作用。对于 pT1N1M0 GC 的早期胃癌患者，应尽可能减少不必要的治疗，以避免过度就医，降低治疗费用，提高生活质量。

此外，研究发现未行辅助化疗、年龄 ≥ 65、ELNC < 16 以及胃底和贲门癌是 pT1N1M0 胃癌术后复发的危险因素。ELNC 是影响早期胃癌患者 OS 的影响因素[26]，这可能与淋巴结微转移存在有关[27]。检查更多的 NLNCs 可以提高潜在转移阳性淋巴结的检出率[28]，ELNC 应被视为提高 GC 患者预后评估准确性的强制性要求，增加 ELNC 是保证精确 TNM 分期的先决条件[29]。对于局部可切除的胃癌患者，NCCN Guidelines 建议胃切除术检查≥16 个淋巴结，本研究证实这同样适用于 pT1N1M0 胃癌。此外，与非贲门癌相比，贲门癌早期预后较差[30]，研究发现可能与 NNMT 富集 AQP5 癌症干细胞的驱动有关[31]。

不足：我们的研究有几个局限性。首先，我们的研究为回顾性分析，可能存在选择偏倚，尽管我们使用了倾向性匹配来解释这一局限性。其次，我们的研究缺乏肿瘤标志物、Hp 感染检测、肿瘤标志物、脉管癌栓神经侵犯、术前影像以及手术方式治疗数据。最后，由于早期胃癌符根治性手术条件的患者相对较少，数据量明显不足，仍需更大样本的研究及前瞻性研究。

5. 结论

总之，即使是早期胃癌，术后系统的辅助治疗也能有效缓解潜在的微转移和未清除的病变。我们的结论支持 pT1N1M0 胃癌患者在胃切除术后至少应接受 ACT 治疗。

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